REMARKS

Applicants respectfully request reconsideration of the present application in view of the following commentary.

I. Status of the Claims

No claim amendments are made in this response. Claims 1-6 and 8 were cancelled previously. Claims 7 and 9-18 are pending.

II. Statement of the Substance of the Interview

Applicants thank Examiner Wu-Cheng Winston Shen and Examiner Thaian Ton for the courtesies extended during an interview with Applicants' representatives Stephen Bent and Yang Tang on July 9, 2009.

The pending obviousness rejection was discussed during the interview, as was the evidence represented in the Rabkin Declaration filed on May 13, 2008. The examiners recommended that Applicants should submit (i) further literature in support that a cytokine expressed from a HSV attenuates HSV replication and/or (ii) additional data that unexpected results are achieved by a cytokine expressed from the claimed HSV.

III. Rejection of Claims under 35 U.S.C. §103(a)

Claims 7, 9-13, 17, and 18 stand rejected over U.S. Patent No. 6,172,047 to Roizman *et al.* in view of Chang *et al., Virology* 185: 437-40 (1991) and Vile *et al., Ann. Oncol.* 5 Suppl. 4:59-65 (1994). Claims 14-16 also are rejected over the combination of Roizman, Chang and Vile in view of PCT Publication No. WO 92/14821 ("McKay") and U.S. Patent No. 5,639,656 ("Wright"). Applicants respectfully traverse each rejection.

A. There was a disincentive to have combined prior-art teachings in the manner posited by the examiner, which defeats the alleged prima facie case under Section 103

Applicants understand the rejection rationale to be that one skilled in the art would have considered it obvious to combine the teachings of Roizman and Chang, regarding mutant HSV, with those of Vile, regarding elimination of tumorigenicity by exogenous expression of a cytokine gene, thereby to arrive at the claimed invention.

To the contrary, however, one of ordinary skill in the art would not have combined the design parameters of (a) long-lasting expression of a transgene for gene-therapy purposes and (b) killing host cells by means of a replicating virus, since these parameters were understood to serve conflicting objectives. Thus, expression of a cytokine requires an intact target cell, while oncolytic therapy by the mutant HSV destroys the target cell. *See* response filed on December 18, 2008, at page 6.

It necessarily follows that the prior art would not have led one of ordinary skill to modify either Roizman or Roizman/Chang to arrive at the claimed invention. With respect to both of the pending Section 103 rejections, therefore, the examiner has not established a *prima facie* case of obviousness, which alone mandates a withdrawal of each rejection.

B. The evidence of record warrants withdrawal of the rejection

Evidencing the art-recognized incongruity of parameters (a) and (b), *supra*, the Rabkin Declaration of record attests to the fact that, at the time of filing, the conventional wisdom in the field included an expectation that cytokines would protect a host from HSV infection and prevent HSV replication in the host. In particular, see Exhibits A, C, F, and H that accompany the Rabkin Declaration. The claimed invention, which requires that a cytokine-expressing HSV infect **and** replicate in tumor cells, thus contravenes what the skilled artisan would have done and expected before the present invention was made.

Nevertheless, Examiner Shen's maintenance of the rejection to date seems focused on his weighing of the declaration evidence, also discussed above. In particular, the Examiner has been inclined to discount the attestations of declarant Rabkin, an expert in the HSV field, largely on the strength of the Examiner's impression that cytokine is expressed only after a herpes simplex virus of

the invention has infected a host cell and, hence, that such expression could not protect the cell from HSV infection.

As a matter of law, however, this impression should not outweigh the declarant's averment regarding the state of the relevant art prior to the claimed invention (see below). As a matter of fact, moreover, the Examiner's impression is not well-conceived because, as was pointed out during the July 9th interview, the oncolytic effects of the claimed invention require that the mutant HSV not only infect a tumor cell but also continue to replicate in that cell and others cells of the tumor. This latter functionality is precisely that which the skilled artisan would have expected cytokine expression to impair. See the Rabkin Declaration, *e.g.*, at paragraph 4.

In this context, Examiner Shen noted during the interview that the exhibits accompanying the Rabkin Declaration were articles showing a protective effect for a cytokine that was not expressed *from* an HSV. Accordingly, the examiner "encourage[d] Applicants to provide evidence(s) supporting that expression of a cytokine gene from an HSV indeed blocks the HSV replication." Interview Summary, continuation sheet.

To address this point, Applicants presently submit a post-filing publication by Ghiasi *et al.*, *J. Virology* 76: 9369-78 (2002) (Exhibit 1 to this response), which reports that expression of cytokine IL-2 ***by*** HSV results in decreased virus replication, both *in vitro* and *in vivo*. *See* the abstract of the Ghiasi article, as well as the text from page 9072 in the left column, second full paragraph, through page 9073 in the left column, and Figures 3 and 4.

In relation to the above-mentioned point about cytokine expression, Examiner Shen also questioned whether "the precise time point when the cytokine gene is expressed from HSV ... would affect the role of expressed cytokine: either (i) preventing HSV replication and thereby preventing oncolytic activity of HSV as Applicant[s] argue[] or (ii) **enhancing oncolytic activity of HSV as taught by Vile et al.**" Interview Summary, continuation sheet (emphasis added).

Applicants would emphasize, however, that a sustainable Section 103 analysis does not question whether one or another of alternative scenarios pertain in fact, since that line of thinking

invites impermissible hindsight. Rather, a proper analysis in this context must question whether, before the claimed invention was made, the skilled artisan had a reason to modify the prior art in some way, effectively bridging the gap between that art and the claimed invention, with a reasonable expectation that such modification would succeed. See MPEP § 2143, elaborating on the U.S Supreme Court's *KSR* opinion.

The Rabkin Declaration attests here to contemporaneous expectations of the relevant art, namely, the field of HSV applications in treating cancer, that militated against combining *in situ* cytokine expression with a oncolytic HSV-design strategy. In evaluating averments directly on point, proffered by a qualified expert in that very field, the examiner should not give preclusive weight to the Vile reference, the teachings of which relate to another field, namely, gene therapy. In a paraphrasing of a pertinent *KSR* holding, this is <u>not</u> an instance where known work in one field of endeavor would have prompted variations of that work in a different field, based on design incentives, if the variations are predictable to one of ordinary skill in the art. MPEP § 2143, item (F) under "Exemplary Rationales." To the contrary, this is an instance where a design *<u>dis</u>*incentive related to a gene-therapy variation, *i.e.*, engineered, tumor-specific expression of cytokines after transient transfection, for which any generalization to the relevant art was wholly unpredictable. *See* 2008 response in the paragraph bridging pages 7 and 8.

C. The claimed invention does achieve results that are unexpected in light of

In light of this last consideration and the additional citation to Ghiasi *et al.* (2002), as requested by the examiner, applicants submit that the evidence of record, including the Rabkin Declaration, amply substantiates the patentability of the claimed invention over any permutation of teachings properly gleaned from the cited prior art. Thus, no rebuttal of the alleged *prima facie* case under Section 103 is either necessary or warranted.

This said, applicants acknowledge Examiner Shen's suggestion that they provide evidence of any "unexpected results (e.g. synergistic effect in killing tumor cells when a cytokine gene is expressed from claimed HSV)" that may "have been observed." Interview Summary, continuation page.

To gauge what would have been unexpected in this regard, applicants note that the Vile publication actually reports an elevation in cytokine expression ***without*** an accompanying change in tumor growth. Thus, Vile *et al.* state:

No statistically significant reduction in tumor growth was seen following injection of any of these cytokine expression plasmids either alone or in combination at the dose tried. However, using rt-PCR to monitor levels of cytokine mRNA, all three cDNAs were expressed in vivo up to 16 days after the single DNA injection....

Page 62, in the right column, at lines 9-14.

Even as propounded by the examiner, therefore, the skilled artisan would not have expected, from Roizman or Roizman/Chang plus Vile, that *in situ* cytokine expression with HSV-mediated oncolysis would achieve better results, vis-à-vis tumor growth, than those observed with oncolysis alone. Yet, a post-filing publication by Liu *et al., Cancer Res.* 65: 1532-40 (2005) (present Exhibit 2), demonstrates that an HSV vector expressing IL-12 is significantly better at inhibiting tumor growth than the HSV vector alone. More specifically, Liu shows that the treatment by "NV1042," the IL-12-expressing HSV vector, significantly increased survival rate (Figure 1A) and decreased the tumor size (Figure 1B) relative to treatment by "NV1023," the HSV vector *sans* cytokine expression. With nothing in Vile or the primary reference(s) that is suggestive of this disparity in results, the skilled artisan necessarily would have deemed the demonstrated enhancement in tumor-growth inhibition, per Liu, to be an unexpected result (or "synergy") achieved with applicants' claimed invention.

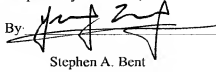
In view of the foregoing, applicants submit (i) that the examiner has not established a *prima facie* case of obviousness and, even were this not the case, (ii) that results achieved with the claimed invention were decidedly unexpected over prior art exemplified by Roizman, Chang, and Vile. Accordingly, withdrawal of the rejection under Section 103 is warranted.

CONCLUSION

Applicants submit that the application is in condition for allowance, and an indication to this effect is requested. Examiner Shen is invited to contact the undersigned directly, should he feel that any issue warrants further consideration.

Respectfully submitted,

Date July 20, 2009

By: 

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The Commissioner is hereby authorized to charge any additional fees, which may be required under 37 C.F.R. §§ 1.16-1.17, and to credit any overpayment to Deposit Account No. 19-0741. Should no proper payment accompany this response, then the Commissioner is authorized to charge the unpaid amount to the same deposit account. If any extension is needed for timely acceptance of submitted papers, then applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of the relevant fee(s) from the deposit account.